Disorders of magnesium metabolism in epilepsy

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Clinical observations in man (Griffiths, 1947; Randall, Rossmeisl, and Bleifer, 1959; Hanna, Harrison, MacIntyre, and Fraser, 1960; Vallee, Wacker, and Ulmer, 1960) and experimental investigations in animals (Kruse, Orent, and McCol- lum, 1932) have shown that magnesium (Mg) depletion causes a marked irritability of the nervous system, eventually resulting in epileptic seizures. The possibility that convulsions may occur in Mg deficiency led some investigators to study the metabolism of this metal in the epilepsies, and a trend to low blood concentrations was usually found (Denis and Talbot, 1921; Blumgarten and Rohdenburg, 1927; Hirschfelder and Haury, 1934, 1935; Haury, 1942; Suter and Klingman, 1955). In successive studies, Hirschfelder and Haury (1935, 1938) found a lowering of Mg and a rise of potassium in the blood of epileptic patients, leading to a definite increase in the K/Mg ratio, proportional to the severity of the disease. Concerning the metabolism of magnesium in the cerebrospinal fluid, Cohen (1927), McCance and Watchorn (1931), and Greenberg and Aird (1938) found in epilepsy the same range of magnesium levels as in other nervous diseases. Hirschfelder and Haury (1938) found low concentrations of Mg in the cerebrospinal fluid of epileptic patients, though the levels were higher than in the blood.

These findings, associated with the fact that Mg is a known depressor of the central nervous system and is involved in several enzymatic processes, including the synthesis of acetylcholine, were not appreciated by some authorities in the field of epilepsy, even when the neurochemistry of this disease was analysed (Tower, 1960).

MATERIAL AND METHODS

Two groups of patients, including 83 cases of epilepsy and 34 of mental disease (mostly schizophrenics), were studied.

The neurological examination was normal in all the epileptic patients and no sign of intracranial hypertension was present. They were from 9 to 56 years old; 44 were males, and 39 females; 67 were white, nine were negroes, and seven were mulattoes. Convulsive manifestations were reported by 71 patients; in 14 the seizures had a centrencephalic pattern and, in 57 they resulted from diffusion of focal discharge; among the latter, 11 patients showed concomitant psychomotor fits. Four patients had only petit mal absences; one had myoclonic petit mal; two had only psychomotor fits. In four cases the seizures were not well characterized from the clinical viewpoint. In one case no epileptic manifestations were reported but the electroencephalogram evidenced a temporal focus.

The epileptic patients were divided into two subgroups. In the first set (cases 1 to 80), blood (79 cases) and cerebrospinal fluid (78 cases) were sampled to determine Mg levels in the period between seizures. In the second set of patients, blood (eight cases) and cerebrospinal fluid (four cases) were sampled immediately after the seizure or during status epilepticus.

Electroencephalograms were recorded in 76 cases. In 25 patients the tracings were normal, in 36 focal abnormalities were recorded, and in 15 the changes were diffuse.

In the mental patients, blood (34 cases) and cerebrospinal fluid (nine cases) were sampled just before and after the electroshock (complete crisis) in the postconvulsive coma.

Cerebrospinal fluid was always collected through cisternal puncture. Magnesium was determined according to the method of yellow titan in alkaline solution, slightly modified (De Jorge, Silva, and Cintra, 1964b). The results were compared with the normal concentrations determined by the same method (De Jorge, Canelas, and Zanini, 1964a).

RESULTS

The results, submitted to conventional statistical analysis, are summarized in Tables I, II, and III.

The existence of hypomagnesaemia in epilepsy, at the interseizure period, was confirmed (Table I). The study of the statistical correlations showed that the blood Mg concentration was lower when the time elapsed after the last convulsion was shorter (Table II).

Although no significant correlation was found with the frequency of fits, our results agree, in a general way, with the findings of Hirschfelder and Haury (1935, 1938). The frequency of fits showed a

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negative correlation with the time after the last seizure, as could be expected (Table II). However, the low level of significance (P ≈ 0.04) of this coefficient may explain the absence of a negative correlation between the Mg content and the frequency of fits. Concerning the cerebrospinal fluid, however, our results did not quite agree with those of the literature since a significant increase of the Mg content in this fluid was found (Table I). An unexpected finding was the positive correlation between the Mg concentration in the blood and in the cerebrospinal fluid (Table II). In this fluid the Mg contents were not significantly correlated with either the frequency or with the time interval after the last seizure.

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\text{TABLE I}
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**AVERAGE CONCENTRATIONS OF MAGNESIUM (mEq./l.) IN THE BLOOD AND CEREBROSPINAL FLUID IN CASES OF EPILEPSY**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of Cases</th>
<th>Mean ± S.D.</th>
<th>Range</th>
<th>Significance of the Difference of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood / Epilepsy</td>
<td>130</td>
<td>2.087 ± 0.067</td>
<td>1.916 - 2.185</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Cerebrospinal fluid / Epilepsy</td>
<td>78</td>
<td>2.419 ± 0.270</td>
<td>1.721 - 2.986</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Blood / Normal</td>
<td>130</td>
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</tr>
</tbody>
</table>

\( t \) test for independent samples assuming unequal variances (Dixon and Massey, 1957).

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\text{TABLE II}
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**BLOOD AND CEREBROSPINAL FLUID MAGNESIUM CONCENTRATIONS IN EPILEPSY CORRELATED WITH THE YEARLY FREQUENCY OF FITS AND THE TIME AFTER THE LAST SEIZURE**

<table>
<thead>
<tr>
<th>Variables</th>
<th>( r )</th>
<th>Significance of Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Mg/frequency of fits</td>
<td>+0.171</td>
<td>0.2&gt;P&gt;0.1</td>
</tr>
<tr>
<td>Blood Mg/time after last seizure</td>
<td>+0.291</td>
<td>0.02&gt;P&gt;0.01</td>
</tr>
<tr>
<td>Cerebrospinal fluid Mg/frequency of fits</td>
<td>+0.081</td>
<td>0.5&gt;P&gt;0.4</td>
</tr>
<tr>
<td>Cerebrospinal fluid Mg/time after last seizure</td>
<td>+0.096</td>
<td>0.5&gt;P&gt;0.4</td>
</tr>
<tr>
<td>Frequency of fits/time after last seizure</td>
<td>-0.245</td>
<td>0.05&gt;P&gt;0.02</td>
</tr>
<tr>
<td>Blood Mg/cerebrospinal fluid Mg</td>
<td>+0.536</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The concentrations of Mg in the blood and in the cerebrospinal fluid of patients with normal, diffuse, or focal electroencephalographic patterns did not show significant differences (Table III). Likewise, the concentrations of blood and cerebrospinal fluid magnesium in post-convulsive cases and in status epileptics were not significantly different from the levels of the same patients at the interseizure period (mean difference in the blood = -0.035 ± 0.297 mEq./l., \( t = 0.327; P < 0.7; \) mean difference in the cerebrospinal fluid = -0.071 ± 0.252 mEq./l., \( t = 0.563; P > 0.6 \)).

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\text{TABLE III}
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**AVERAGE CONCENTRATIONS OF MAGNESIUM IN THE BLOOD AND CEREBROSPINAL FLUID IN DIFFERENT ELECTROENCEPHALOGRAPHIC PATTERNS AND SIGNIFICANCE OF THE DIFFERENCES BETWEEN THEM**

<table>
<thead>
<tr>
<th>E.E.G.</th>
<th>No.</th>
<th>Mean ± S.D.</th>
<th>Significance of the Differences (( t ))</th>
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</thead>
<tbody>
<tr>
<td>Blood</td>
<td>15</td>
<td>1.895 ± 0.231</td>
<td>Focal = 0.022</td>
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<tr>
<td>Cerebrospinal fluid</td>
<td>14</td>
<td>2.395 ± 0.472</td>
<td>Diffuse = 0.035</td>
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<tr>
<td>Normal</td>
<td>25</td>
<td>1.836 ± 0.189</td>
<td>Focal = 0.858</td>
</tr>
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</table>

\( t \) As the whole level of significance adopted was \( a = 5 \%, \) we worked in the individual independent tests, with the level \( a = 5/3 \% \) (Steel and Torrie, 1960).

In the second group of patients, after electroshock-induced convulsions the Mg contents showed an increase both in the blood and in the cerebrospinal fluid (mean difference in the blood = +0.472 ± 0.201; \( t = 13.681; P < 0.001 \); mean difference in the cerebrospinal fluid = +0.307 ± 0.121; \( t = 7.595; P < 0.001 \)).

**DISCUSSION**

Notwithstanding the numerous studies on Mg metabolism, their interpretation is still obscure. Magnesium is the fourth most abundant cation of the human body. If only the intracellular component is analysed, Mg is the second most frequent cation, following potassium (MacIntyre, 1959; Clough, 1960). The views on the interpretation of the Mg depletion syndrome are still conflicting, the condition being ascribed either to a fall of the intracellular Mg, with a lowering of the intracellular/extracellular ratio (Clough, 1960), or to a depletion of the extracellular concentration, in a way very similar to the behaviour of sodium (Suter and Klingman, 1955).

If an inhibition of acetylcholine synthesis by Mg was assumed to occur at the cerebral level, as it happens at the periphery (Del Castillo and Engbaek, 1954; Hutter and Kostial, 1954; Maurat, 1958), then it could be understood why, in the Mg depletion syndrome and in epilepsy, acetylcholine is more
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